The experience of UK patients with bladder cancer during the COVID-19 pandemic

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When their first antimuscarinic has failed, why not take a different path?

astellas

Prescribing another antimuscarinic may be of minimal benefit after the first has failed.[1] So why not choose another route? BETMIGA is in a different class, relaxing the bladder via β_3-adrenoceptors.[2] It can be just as effective as an antimuscarinic, but it doesn't have the same side-effect profile.[3]

BETMIGA is indicated for symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder (OAB) syndrome.[2]

Prescribing information: BETMIGA™ (mirabegron)

For full prescribing information, refer to the Summary of Product Characteristics (SPC)

Presentation: BETMIGA prolonged-release tablets containing 25 mg or 50 mg mirabegron.

Indication: Symptomatic treatment of urgency, increased micturition frequency and/or urgency incontinence as may occur in adult patients with overactive bladder (OAB) syndrome.

Posology and administration: The recommended dose is 50 mg orally once daily in adults (including elderly patients). Mirabegron should not be used in paediatrics. A reduced dose of 25 mg once daily is recommended for special populations (please see the full SPC for information on special populations). The tablet should be taken with liquids, swallowed whole and is not to be chewed, divided, or crushed. The tablet may be taken with or without food.

Contraindications: Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the SPC. Severe uncontrolled hypertension defined as systolic blood pressure ≥ 180 mm Hg and/or diastolic blood pressure ≥ 110 mm Hg.

Warnings and Precautions: Renal impairment: BETMIGA has not been studied in patients with end stage renal disease (GFR < 15 mL/min/1.73 m^2 or patients requiring haemodialysis) and, therefore, it is not recommended for use in this patient population. Data are limited in patients with severe renal impairment (GFR 15 to 29 mL/min/1.73 m^2); based on a pharmacokinetic study (see section 5.2 of the SPC) a dose reduction to 25 mg is recommended in this population. This medicinal product is not recommended for use in patients with severe renal impairment (GFR 15 to 29 mL/min/1.73 m^2) concomitantly receiving strong CYP3A inhibitors (see section 4.5 of the SPC). Hepatic impairment: BETMIGA has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) and, therefore, it is not recommended for use in this patient population. This medicinal product is not recommended for use in patients with moderate hepatic impairment (Child-Pugh B) concomitantly receiving strong CYP3A inhibitors (see section 4.5 of the SPC). Hypertension: Mirabegron can increase blood pressure. Blood pressure should be measured at baseline and periodically during treatment with mirabegron, especially in hypertensive patients. Data are limited in patients with stage 2 hypertension (systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥100 mm Hg). Patients with congenital or acquired QT prolongation: BETMIGA, at therapeutic doses, has not demonstrated clinically relevant QT prolongation in clinical studies (see section 5.1 of the SPC). However, since patients with a known history of QT prolongation or patients who are taking medicinal products known to prolong the QT interval were not included in these studies, the effects of mirabegron in these patients is unknown. Caution should be exercised when administering mirabegron in these patients. Patients with bladder outlet obstruction and patients taking antimuscarinics medicinal products for OAB: Urinary retention in patients with bladder outlet obstruction (BOO) and in patients taking antimuscarinic medicinal products for the treatment of OAB has been reported in postmarketing experience in patients taking mirabegron. A controlled clinical safety study in patients with BOO did not demonstrate increased urinary retention in patients treated with BETMIGA; however, BETMIGA should be administered with caution to patients with clinically significant BOO. BETMIGA should also be administered with caution to patients taking antimuscarinic medicinal products for the treatment of OAB.

Interactions: Caution is advised if mirabegron is co-administered with medicinal products with a narrow therapeutic index and significantly metabolised by CYP2D6. Caution is also advised if mirabegron is co-administered with CYP2D6 substrates that are individually dose titrated. In patients with mild to moderate renal impairment or mild hepatic impairment, concomitantly receiving strong CYP3A inhibitors, the recommended dose is 25 mg once daily. For patients who are initiating a combination of mirabegron and digoxin (P-gp substrate), the lowest dose for digoxin should be prescribed initially (see the SPC for full prescribing information). The potential for inhibition of P-gp by mirabegron should be considered when BETMIGA is combined with sensitive P-gp substrates. Increases in mirabegron exposure due to drug-drug interactions may be associated with increases in pulse rate.

Pregnancy and lactation: BETMIGA is not recommended in women of childbearing potential not using contraception. This medicinal product is not recommended during pregnancy. BETMIGA should not be administered during breast-feeding.

Undesirable effects: Summary of the safety profile: The safety of BETMIGA was evaluated in 8433 patients with OAB, of which 5648 received at least one dose of mirabegron in the phase 2/3 clinical program, and 622 patients received BETMIGA for at least 1 year (365 days). In the three 12-week phase 3 double blind, placebo controlled studies, 88% of the patients completed treatment with this medicinal product, and 4% of the patients discontinued due to adverse events. Most adverse reactions were mild to moderate in severity. The most common adverse reactions reported for patients treated with BETMIGA 50 mg during the three 12-week phase 3 double blind, placebo controlled studies are tachycardia and urinary tract infections. The frequency of tachycardia was 1.2% in patients receiving BETMIGA 50 mg. Tachycardia led to discontinuation in 0.1% patients receiving BETMIGA 50 mg. The frequency of urinary tract infections was 2.9% in patients receiving BETMIGA 50 mg. Urinary tract infections led to discontinuation in none of the patients receiving BETMIGA 50 mg. Serious adverse reactions included atrial fibrillation (0.2%). Adverse reactions observed during the 1-year (long term) active controlled (muscarinic antagonist) study were similar in type and severity to those observed in the three 12-week phase 3 double blind, placebo controlled studies. Adverse reactions: The following list reflects the adverse reactions observed with mirabegron in the three 12-week phase 3 double blind, placebo controlled studies. The frequency of adverse reactions is defined as follows: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000) and not known (cannot be established from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. The adverse events are grouped by MedDRA system organ class. *Infections and infestations:* Common: Urinary tract infection, Uncommon: Vaginal infection, Cystitis. *Psychiatric disorders:* Not known (cannot be estimated from the available data): Insomnia*, Confusional state*. *Nervous system disorders:* Common: Headache*, Dizziness*. *Eye disorders:* Rare: Eyelid oedema. *Cardiac disorders:* Common: Tachycardia, Uncommon: Palpitation, Atrial fibrillation. *Vascular disorders:* Very rare: Hypertensive crisis*. *Gastrointestinal disorders:* Common: Nausea*, Constipation*, Diarrhoea*, Uncommon: Dyspepsia, Gastritis, Rare: Lip oedema. *Skin and subcutaneous tissue disorders:* Uncommon: Urticaria, Rash, Rash macular, Rash papular, Pruritus, Rare: Leukocytoclastic vasculitis, Purpura, Angioedema*. *Musculoskeletal and connective tissue disorders:* Uncommon: Joint swelling. *Renal and urinary disorders:* Rare: Urinary retention*. *Reproductive system and breast disorders:* Uncommon: Vulvovaginal pruritus. *Investigations:* Uncommon: Blood pressure increased, GGT increased, AST increased, ALT increased. * signifies adverse reactions observed during post-marketing experience. Prescribers should consult the SPC in relation to other adverse reactions.

Overdose: Treatment for overdose should be symptomatic and supportive. In the event of overdose, pulse rate, blood pressure, and ECG monitoring is recommended.

Basic NHS Cost: BETMIGA 50 mg x 30 = £29, BETMIGA 25 mg x 30 tablets = £29

Legal classification: POM

Marketing Authorisation number(s): EU/1/12/809/001 – 018

Marketing Authorisation Holder: Astellas Pharma Europe B.V. Sylviusweg 62. 2333 BE Leiden. The Netherlands.

Date of Preparation of Prescribing information: June 2019

Job bag number: BET_2019_0023_UK

Further information available from: Astellas Pharma Ltd, Medical Information: 0800 783 5018. For full prescribing information, please see the Summary of Product Characteristics, which may be found at www.medicines.org.uk

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to Astellas Pharma Ltd. on 0800 783 5018

October 2020

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Research Communication

The experience of UK patients with bladder cancer during the COVID-19 pandemic: a survey-based snapshot

The COVID-19 pandemic has placed unprecedented strain on healthcare systems worldwide with the requirement to treat large influxes of infected patients, many of whom require respiratory support. Healthcare systems have had to redirect resources and redeploy staff away from routine diagnostic, treatment and follow-up services. The NHS in the UK is no different, and cancer services have undergone significant disruption to create the emergency capacity to tackle the pandemic. As a charity that endeavours to support bladder cancer (BC) patients and improve outcomes, Action Bladder Cancer UK (ABC UK, Tetbury, UK) designed and administered an online survey to investigate the prevalence of such disruption.

Using the SurveyMonkey platform (San Mateo, CA, USA), the survey was launched on 22 April 2020 (approximately 10 days after the peak of UK COVID-19 cases) and closed on 22 July 2020. BC patients were directed to the survey via the ABC UK website (http://actionbladdercanceruk.org/), ABC UK Patient Support Groups, and social media platforms. In addition to the collection of anonymized demographic and tumour-specific characteristics, the first three digits of each postcode were converted into area type using Office for National Statistics postcode data and categorized as rural, urban city and town, and urban major conurbation. Associations between area type and disruption were assessed using the chi-squared test. The analysis of these data was approved by the King's College London Research Ethics Office.

In the time from inception to completion, 156 patients with BC responded. Over 94% of respondents lived in England, although there was geographical reach from all of the UK. A total of 34% of patients were from rural areas, 29% were from urban cities and towns, and 22% were from major conurbations such as West Yorkshire, Greater Manchester and Greater London (15% did not submit postcodes). Almost 80% of respondents were aged 60 years or older and more than 68% were men. Approximately 71% of respondents had non-muscle-invasive BC (NMIBC), 22% had muscle-invasive BC (MIBC), and 3% had a diagnosis of advanced/metastatic disease.

Across all groups, 49% of patients described disruption to their treatment or follow-up (delays, postponements, or cancellations/curtailments), while 33% of patients indicated no change, with treatment and follow-up proceeding as normal. The majority of the remaining 18% of patients were scheduled for follow-up several months in the future and had not yet been informed of any changes. There was no association between area type (rural/urban) and disruption to treatment. This lack of association remained when stratified by NMIBC vs MIBC/advanced disease.

In patients who described disruption, 50% had received a telephone call to inform them, 27% had received a letter, 2% had received a text message, and 21% had contacted the hospital themselves; 33% reported that the pandemic had made it more difficult to communicate with their urology team.

Eight respondents were awaiting their initial transurethral resection of bladder tumour (TURBT); for two of these patients, TURBT had been delayed or postponed (Table 1). Sixteen patients were awaiting a subsequent TURBT (for re-resection or recurrence); for six of these patients, TURBT had been delayed or postponed. Ninety-seven patients described being under cystoscopic surveillance, 85% of whom had NMIBC and 14% MIBC (one patient did not specify their disease status). A total of 51 patients (53%) reported a delay or postponement to their surveillance (Table 1). Of 53 patients with NMIBC undergoing courses of intravesical therapy, 37 (70%) described delays, postponements or curtailments in treatment (Table 1).

Seventeen patients were awaiting cystectomy, of whom nine had been notified of a postponement in their surgery, and three had been notified of cancellation of their surgery (Table 1). Two patients' treatment plans changed from cystectomy to radiotherapy; there were no patients who changed from radiotherapy to cystectomy, and no patients described disruption to radiotherapy or neoadjuvant chemotherapy (Table 1).

Eight patients described undergoing treatment regimens for locally advanced or metastatic disease (adjuvant chemotherapy or chemotherapy only); five of these patients described disruption to the administration of chemotherapy (Table 1).

Regarding COVID-19 itself, 67 respondents (43%) had been advised to shield, and the majority of the remainder felt that they should have been advised to shield and shielded anyway.

Table 1 Changes to treatment due to COVID-19 based on a survey of 156 respondents.

Treatment	Status	*n*	%
First TURBT (n = 8)	Postponed	2	25.0
	Cancelled	0	0.0
	Going ahead as planned	6	75.0
Subsequent TURBT (n = 16)	Postponed	6	37.5
	Cancelled	3	18.8
	Going ahead as planned	7	43.8
Cystectomy (n = 17)	Postponed	9	52.9
	Cancelled	3	17.7
	Going ahead as planned	5	29.4
Intravesical therapies (BCG and mitomycin; n = 53)	Postponed	28	52.8
	Cancelled	9	17.0
	Going ahead as planned	10	18.9
	Other/missing	6	11.3
Cystoscopic surveillance (n = 97)	Postponed	40	41.2
	Cancelled	11	11.3
	Going ahead as planned	33	34.0
	Other/missing	13	13.4
Neoadjuvant chemotherapy (prior to cystectomy or radiotherapy; n = 3)	Postponed	0	0.0
	Cancelled	0	0.0
	Going ahead as planned	2	66.7
	Other/missing	1	33.3
Adjuvant chemotherapy (after cystectomy or radiotherapy; n = 6)	Postponed	3	50.0
	Cancelled	1	16.7
	Going ahead as planned	2	33.3
	Other/missing	0	0.0
Chemotherapy only (n = 2)	Postponed	0	0.0
	Cancelled	1	50.0
	Going ahead as planned	1	50.0
	Other/missing	0	0.0

TURBT, transurethral resection of bladder tumour.

A total of 76% of patients expressed some concern about attending hospital for their treatment and follow-up appointments, and approximately 64% described that safety precautions for themselves and for staff would make them feel safer when attending.

The outputs of this survey have demonstrated the considerable disruption to the care of BC patients in the UK during the COVID-19 pandemic. Notably, the level of disruption was not significantly different between patients from different types of geographical area (e.g. rural or urban), with the survey capturing a representative sample of the BC population: the majority of respondents were both male and aged >60 years, and approximately 71% were NMIBC patients.

It was also interesting to observe that, although fewer than half of the patients were advised to shield, the majority of patients did so anyway. This response is reflected in the high levels of concern and/or anxiety reported by patients regarding returning to hospital to continue treatment and/or follow-up.

A survey of this nature has a number of limitations. Although the patient demographics accurately reflect those of the UK BC population, this remains a relatively small study using an unvalidated questionnaire. The survey was more likely to be completed by existing patients with BC who are already engaged with ABC UK, rather than newly diagnosed patients who may not yet be aware of the charity's work. Furthermore, local or regional patterns have not been captured comprehensively, and more nuanced responses to the survey may have been obtained via telephone interview.

Patients with BC in the UK are not alone in experiencing disruption to their care during the pandemic [1,2]. Some of these disruptions will have been justified in order to protect patients from COVID-19 itself or from additional complications of specific treatments in the environment of the pandemic [2–4]; yet much disruption will have directly resulted from the emergency redeployment of healthcare services to tackle the pandemic. Our survey appears to demonstrate that both MIBC and NMIBC patients have been equally affected by delays, postponements and cancellations during the COVID-19 pandemic. Hence, despite a plethora of recommendations from a number of sources outlining reasonable patient prioritization strategies [2,5–7], these strategies may not have been developed and circulated quickly enough or enacted rapidly enough at or around the peak of the UK pandemic to have made a perceivable difference to patients. Given the overwhelming nature of the pandemic on the whole of society, this is understandable. However, it is critical that the BC clinical and academic community maintains an 'institutional memory' should similar circumstances ensue in the form of a second wave of COVID-19, or as a separate threat. Now is the time to plan effective contingent ways of working and agree upon protocols that minimize the disruption to high-quality bladder cancer care should either scenario become reality; considerable evidence is available to inform such strategies [5,6], including publications available at the following websites:

https://www.bjuinternational.com/bjui-blog/covid-19-collection-of-urology-papers/

https://www.europeanurology.com/covid-19-resource

https://uroweb.org/wp-content/uploads/Covid-19-EAU-NMIBC-Recommendations.pdf

https://ukcoronaviruscancermonitoring.com/.

Notwithstanding, the true success of any strategy in the cancer setting can only be appropriately assessed several years downstream in terms of clinical outcomes; potential health-related quality-of-life deficits should not be forgotten, and we are planning follow-up surveys to attempt to capture the physical and psychological burden of the treatment disruptions and postponements. Furthermore, we should be aware that new suspected cancer referrals have also dramatically reduced during the pandemic [8], and so there is a long road to recovery ahead and for none more so than patients with BC.

Conflicts of Interest

R. T. Bryan has contributed to advisory boards for Olympus Medical Systems and Janssen, and undertakes research funded by UroGen Pharma and QED Therapeutics. ABC UK is a UK registered charity and receives income from a variety of sources including public donations and grants, as well as educational grants from corporate supporters. In 2020 to date, ABC UK has received educational grants from Bristol Myers Squibb, Janssen-Cilag Ltd, Merck Serono Limited and Pfizer UK.

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Abbreviations: ABC UK, Action Bladder Cancer UK; BC, bladder cancer; TURBT, transurethral resection of bladder tumour.